REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 1-4, 15-26 and 23-26 are pending in the present action.

DOUBLE PATENTING

On pages 2-3 of the Office Action, the Examiner provisionally rejected the claims 1-34 on the grounds of non-statutory obviousness-type double patenting in view of claims 1-31 of co-pending United States Patent Application No. 10/664,803.

The Examiner also provisionally rejected claims 1-34 on the grounds of non-statutory obviousness-type double patenting in view of claims 1-38 of co-pending United States Patent Application No. 11/094,493.

In an effort to expedite prosecution of the present application, submitted herewith is a terminal disclaimer for United States Patent No. 10/664,803. Applicants respectfully traverse the double patenting rejection based upon Application No. 11/094,493.

Claims 1-38 of Application No. 11/094,493 recite a pharmaceutical dosage form exhibiting a controlled release of a first active ingredient and an immediate release of a thiazolidinedone derivative wherein the dosage form exhibits a "significantly higher bioavailability" of the thiazolidinedone derivative than conventional immediate release thiazolidinedone derivatives. It is respectfully submitted that the "significantly higher bioavailability" limitation of claims 1-38 renders these claims patentably distinct from the claims in the pending application.

The claims in the pending application require specific release profile and stability profile for the immediate release pioglitazone layer. As explained in the pending application, Applicants have discovered a unique oral dosage form that provides therapeutic levels for metformin and pioglitazone based upon once a day dosing. During the development of this dosage form, Applicants needed to resolve the release and stability concerns for two drugs with vastly different solubilities and different stabilities. A number of experiments were conducted that evaluated many different formulations. Based upon the research conducted it was determined the a composition as described in Example 6 produced a suitable once a day dosage form by releasing the pioglitazone in an appropriate time frame, i.e. within 45 minutes, and maintained the stability of the pioglitazone at room temperature and higher.

Subsequent to this discovery, Applicants discovered that the use of certain excipients in the thiazolidinedone layer could significantly improve the bioavailability of the thiazolidinedone derivative. Not all immediate release thiazolidinedone coatings exhibit the significantly higher bioavailability. This fact is demonstrated on page 32 of Application No. 11/094,493. The tables at the bottom of page 32 compare Reference Examples 2 and 3 which have a metformin core, a seal coat and immediate release thiazolidinedione coat to Example 2 which also has the same structure but different immediate release thiazolidinedione coat composition. The data shows that bioavailability of the thiazolidinedione derivative is dependant upon the composition of the thiazolidinedone coat. More specifically if certain excipients are included in the thiazolidinedione coat, the bioavailability of the thiazolidinedione derivative can be

significantly increased.

Applicants respectfully submit that this discovery of a formulation that exhibits "significantly higher bioavailabilty", a limitation of claims 1-38 of Application No. 11/094,493, renders claims 1-38 patentably distinct from the claims in the present application which are directed to a formulatiuon with specific release and stability profiles for the immediate release thiazolidinedione coat.

Based upon the terminal disclaimer submitted herewith and the above remarks, it is respectfully requested that the provisional double patenting rejections be withdrawn.

35 U.S.C. § 112

On page 4 of the Office Action, the Examiner rejected claims 30-32 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the claims contained subject matter not described in such a way as to reasonably convey to one skilled in the art that the inventors(s), at the time the application was filed, had possession of the claimed invention.

Applicants do not believe this rejection is correct because all the elements of the rejected claims can be found on pages 3-4 of the present application. However, in an effort to expedite prosecution, these claims have been canceled without prejudice.

On pages 4-8 of the Office Action, the Examiner discusses in detail claims 1-34. Based upon the entire reading of the 35 U.S.C.§ 112 section of the Office Action, it appears the initial rejection of claims 30-32 under 35 U.S.C. § 112, first paragraph, may have been a typographical error and the rejection is really of claims 1-34. Assuming that the rejection is for claims 1-34, Applicants again do not believe the rejection is correct because the

elements of claims 1-34 are fully described on pages 3-4 of the present specification with an embodiment exemplified in Example 6. However, in an effort to expedite prosecution of the present application, Applicants have limited the claims to a dosage form that contain metformin or a pharmaceutically acceptable salt thereof in the controlled release core and pioglitazone or a pharmaceutically acceptable salt thereof in the immediate release layer. No new matter is added by this amendment. Support can be found in Example 6 on pages 23-27 of the present specification.

Based upon the foregoing amendments it is respectfully submitted that the rejection of the claims under 35 U.S.C. § 112, first paragraph, have been overcome and it is respectfully requested that the rejection be withdrawn.

35 U.S.C. § 103(a)

On pages 8-11 of the Office Action, the Examiner rejected claims 1-34 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Vergez et al., United States Published Patent Application No. 2006/0204578 ("Vergez").

In response to this rejection Applicants have amended the claims to specifically indicate that the claimed dosage form requires a controlled release core that contains only one active ingredient, metformin, and an immediate release coating that contains pioglitazone. The claims have also been amended to indicate that at least 85% of the pioglitazone is released within 45 minutes when tested according to a specific United States Pharmacopeia (USP) methodology and that the total amount of pioglitazone related compounds or impurities in the dosage form after storage at 40°C and 75% relative humidity for three months is not more than 0.6% with no individual impurity

exceeding 0.25%. No new matter is added by these amendments. Support can be found on page 4, lines 17-27 and Example 6 on pages 23-27 of the present specification and claims 1, 13 and 16 as originally filed.

It is respectfully submitted that the present claims are patentable over the Vergez reference because the present claims require a controlled release core that contains only one pharmaceutically active ingredient, specifically metformin and an immediate release pioglitazone layer. The Vergez reference is directed to a dosage form that contains two (2) different active ingredients in the core and both active ingredients are released in a controlled manner. *See*: paragraphs 2 and 15 of the Vergez reference. The fact that the pending claim require only one drug in the core and only one drug that is released in a controlled manner and the Vergez reference requires two drugs in the core and two drugs released in a controlled manner, renders the Vergez reference non analogous art to the invention recited in the pending claims.

Applicants do not dispute the Examiner's contention that paragraphs 43 and 63 of the Vergez reference suggest the application of an immediate release layer to the Vergez two drug controlled release core, however, this suggestion does not negate the overwhelming teaching of the Vergez reference to employ two (2) drugs in the core.

Further, there is no suggestion or guidance to an individual of ordinary skill on how to prepare a once a day metformin and piogltiazone dosage form. Metformin and pioglitazone are only mention in a long list of possible drugs. *See*: paragraphs 86-87 and 148-157 of the Vergez reference. There is no guidance on how to combine these drugs nor any guidance on which drug to place in the controlled release core and which drug to

place in the immediate release layer. The only guidance for formulating a pioglitazone dosage form provided by the Vergez reference can be found in Example 7, ¶ 190 of the Vergez reference. This Example combines atorvastatin and pioglitazone in a dosage form core and releases both drugs in a controlled or sustained manner, not an immediate release manner as recited in the pending claims. Based upon this teaching an individual of ordinary skill would be lead to place the pioglitazone in a controlled release core, not an immediate release coating as required by the present claims.

On page 10, first full paragraph of the Office Action, the Examiner states:

> One of ordinary skill in the art at the time of the invention would have been movitated to include the antidiabetic with the smaller dosage (lower MW) in the outer layer since it is intended for immediate release and has a quicker dissolution profile. Likewise, the artisan would have been motivated to include the larger dosage (higher MW) antidiabetic in the core since it has slower dissolution profile and would take longer for it to erode or dissolve.

Applicants respectfully disagree with this statement because the Vergez reference does not teach or suggest such a dosage form anywhere in the entire reference. As stated previously, the Vergez reference overwhelmingly teaches placing two drugs in the core and releasing both drugs from the core in a controlled manner. There is no suggestion to completely eliminate one drug from the core without the improper benefit of hindsight.

The above quoted Examiner's statement about dissolution profile and molecular weights supports patentability of the present claims. Pioglitazone has a molecular weight of 365.4 (392.9 for the hydrochloride salt) and is practically insoluble in water. Merck Index 13th ed. entry 7533 (a copy is attached as Exhibit A). *See also:* Vergez reference ¶ 157. Metformin has a molecular weight of 129.2 (165.6 for the hydrochloride salt) and is

freely soluble in water. Merck Index 13th ed. entry 5963 (a copy is attached as Exhibit B). *See also*: Vergez reference ¶ 152. If the Examiner's contention that an individual of ordinary skill would place the lower molecular weight and more soluble component in the immediate release coating and the higher molecular weight and slower dissolving component in the controlled release core is correct, then the present claims are patentable because the Applicants did the exact opposite of what an individual of ordinary skill would do. As recited in the pending claims, Applicants put the higher molecular weight and less soluble component in the immediate release coating and the lower molecular weight and more soluble component in the controlled release core.

Finally, Applicants respectfully submit that the pending claims are patentable over the Vergez reference because the Vergez reference fails to provide any guidance or suggestions for designing a stable once a day oral dosage form the delivers therapeutic levels of both metfomin and pioglitazone to a patient as recited in the pending claims. Metformin and pioglitazone have different chemical and physical properties. Applicants have discovered a suitable once a day combination oral dosage form can be prepared for these vastly different drugs by placing the insoluble pioglitazone in an immediate release layer and the soluble metformin in the controlled release portion. Applicants further discovered that at least 85% of the pioglitazone should be released within 45 minutes in order to insure the pioglitazone is available to the patient at an appropriate time to provide the necessary therapeutic amounts.

Still further, Applicants need to address the stability issues for pioglitazone. As evidenced by Exhibit C, which is a supplier brochure for pioglitazone, it was known that

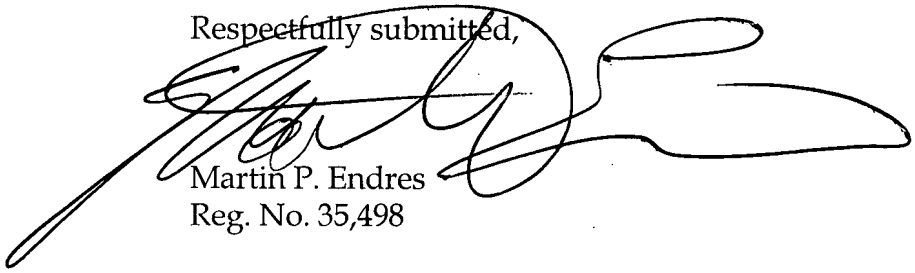
pioglitazone has stability concerns. Specifically, Exhibit C recommends that pioglitazone be stored at -20°C to insure stability. Applicants have surprisingly discovered that the selection of excipients for the immediate release pioglitazone coat, including the solvents for application of the immediate release pioglitazone coat, can produce a stable immediate release pioglitazone coat for a once a dosage form, even when stored at room temperature of higher.

It is respectfully submitted that the dosage form recited in the pending claims is not the product of a mere matter of design choice but the result of many hours of research to design a stable once a day dosage form that provides therapeutic levels of metformin and piogltizone to a patient. The Vergez reference provides no guidance to an individual to arrive at the invention recited in the present claims, nor even hints of the many problems the Applicants encountered and overcame during their research.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

It is believed that no fee is required for submission of this response because it is being mailed before the three month deadline, September 11, 2007. If a fee is due, the Commissioner is authorized to charge our deposit account, Account No. 08-1540.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on Sept. 11, 2007